REVIEW

β-Blocker Use for the Stages of Heart Failure

MARC KLAPHOLZ, MD

The 2005 American Heart Association/American College of Cardiology heart failure (HF) guidelines contributed to a renewed focus on "at-risk" patients and emphasized HF as a progressive disease. Patient categorization by stages focused attention on customization of therapy to achieve optimal, evidence-based treatments across the HF continuum. Therapy for risk factors that predispose patients to left ventricular dysfunction or other symptoms may help reduce HF development. β-Blockers are valuable for treatment of HF; however, the class is heterogeneous, and proper β-blocker selection for each HF stage is important. β-Blockers have been used routinely to treat patients with stage A HF with hypertension. Recent controversy regarding the detrimental effects that some β-blockers have on metabolic parameters has raised inappropriate concerns about the use of any β-blocker for diabetes. β-Blockade is standard therapy for the patient with stage B HF who has had a myocardial infarction, but few data are available concerning use in asymptomatic patients with left ventricular dysfunction. Additionally, β-blockers are part of the core therapy for stage C HF and selected patients with stage D HF. This review examines the role and use of β-blockers in each HF stage through an evidence-based approach to provide better understanding of their importance in this progressive disease. PubMed searches (1980-2008) identified large clinical trials that evaluated cardiovascular events and outcomes in any HF stage or hypertension. Search terms were *heart failure, hypertension, β-blocker, ACEI, ARB, and calcium channel blocker* AND *blood pressure coronary artery disease, diabetes, efficacy, left ventricular dysfunction, metabolism, mortality, myocardial infarction,* or *stroke*.

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ACC/AHA = American College of Cardiology/American Heart Association; ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ASCOT-BPLA = Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm; BEST = β-Blocker Evaluation of Survival Trial; CAD = coronary artery disease; CAPRICORN = Carvedilol Post-Infarct Survival Control in LV Dysfunction; CI = confidence interval; COMET = Carvedilol or Metoprolol European Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; HbA_{1c} = hemoglobin A_{1c}; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; HOPE = Heart Outcome Prevention Evaluation; LVD = left ventricular dysfunction; LVEF = LV ejection fraction; LVSD = LV systolic dysfunction; MI = myocardial infarction; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NYHA = New York Heart Association; RR = relative risk; SAVE = Survival and Ventricular Enlargement; SOLVD = Studies of Left Ventricular Dysfunction

Heart failure (HF) is classically a progressive disease initiated by injury to the myocardium that produces changes in the structure and function of the left ventricle. With time, elevated adrenergic tone and neurohormonal activity mediate progressive left ventricular dysfunction (LVD) and structural remodeling marked by dilatation, hypertrophy, and declining LV ejection fraction (LVEF).[1,2] The level of adrenergic activation correlates strongly with the risk of HF progression and death.[3-5] Angiotensin-converting enzyme (ACE) inhibition, aldosterone blockade, and β-blockade have been shown to attenuate the remodeling and systemic effects of adrenergic and neurohormonal activation. Three β-adrenergic blockers—bisoprolol, carvedilol, and metoprolol succinate—have been shown to reduce mortality and morbidity in patients with HF resulting from LV systolic dysfunction (LVSD).[6-9]

The clinical syndrome of HF is usually marked by chronic fatigue, exercise intolerance, and remitting episodes of exacerbation. Signs on physical examination are specific.[8] Principal symptoms of HF are dyspnea at rest or on exertion and fatigue. Physical findings are often related to volume overload, such as pulmonary congestion or peripheral edema.[8] In patients with a predominant low-output syndrome, physical findings may be more subtle. Symptoms and physical findings can fluctuate throughout the course of the disease, although there is often an inexorable progression that leads to worsening signs and symptoms and end-organ compromise, particularly in the kidneys.[8,10]

The American College of Cardiology/American Heart Association (ACC/AHA) developed a classification scheme for HF, beginning with patients at risk for developing HF (pre-HF) and ending with patients who have refractory end-stage HF (Figure 1).[8] Patients are assigned to these stages on the basis of the presence of risk factors, cardiac structural and/or functional abnormalities, and symptoms. Categorization of patients by stages focuses attention on prevention and customization of therapy to achieve optimal, evidence-based treatments for each stage. Before the ACC/AHA stages were published, clinicians exclusively used the New York Heart Association (NYHA) classification system (Table 1).[11] However, the ACC/AHA stages are important in that they address the presence of structural cardiac disease and recognize risk factors as important contributors to morbidity and mortality in patients with HF.[8]

Initiating therapy for HF risk factors may help reduce the development of structural abnormalities and subsequent

From the Division of Cardiology, University of Medicine and Dentistry of New Jersey, Newark.

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Individual reprints of this article are not available. Address correspondence to Marc Klapholz, MD, University of Medicine and Dentistry of New Jersey, Medical Science Bldg, 185 S Orange Ave, Floor I, Room 536, Newark, NJ 07103-2714 (klapholz@umdnj.edu).

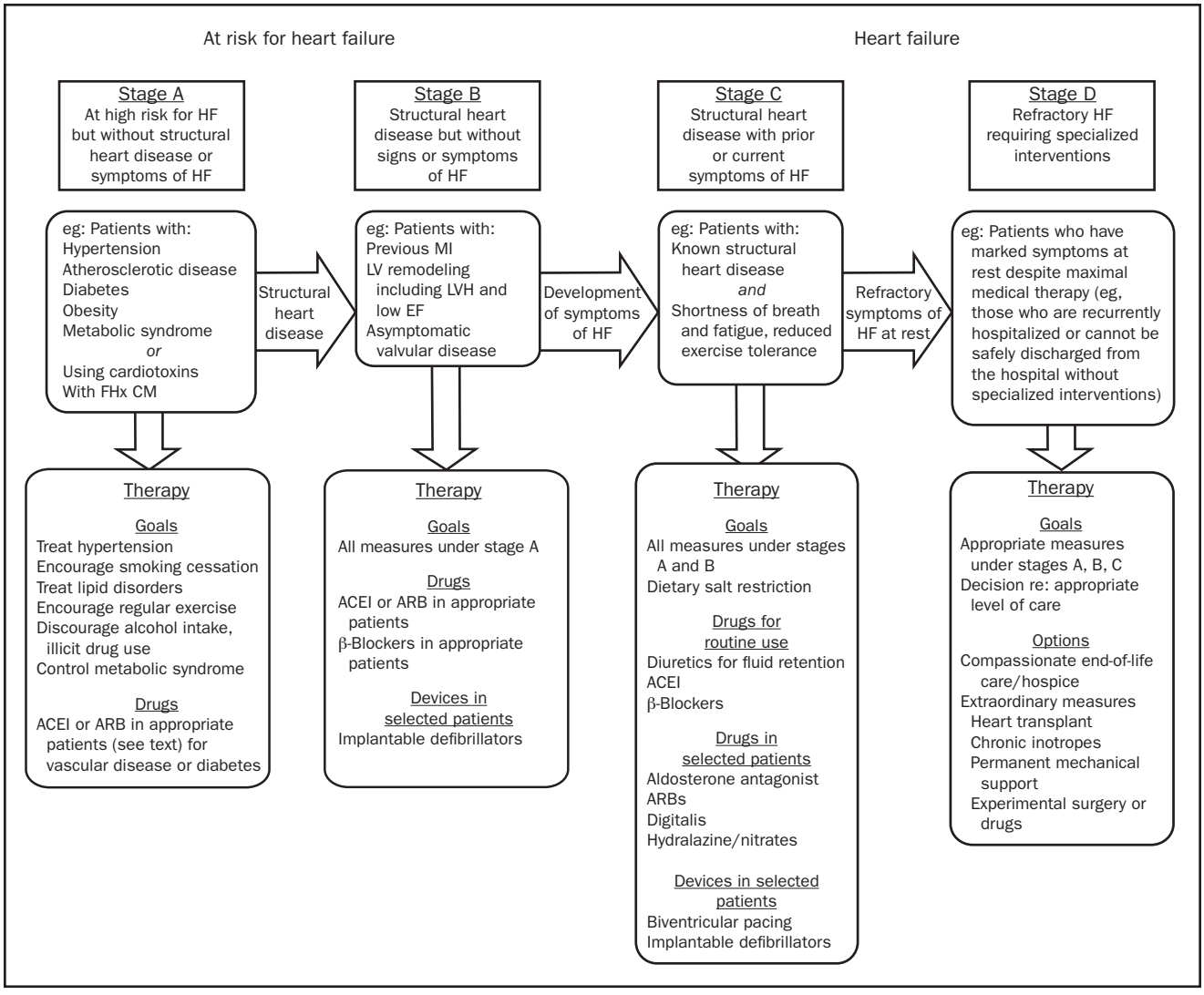

FIGURE 1. American College of Cardiology/American Heart Association 2005 classification of heart failure (HF). ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; EF = ejection fraction; FHx CM = family history of cardiomyopathy; LV = left ventricular; LVH = LV hypertrophy; MI = myocardial infarction. From *Circulation*,[8] with permission.

symptoms. Blocking or limiting neurohormonal activation and its effects is especially important in retarding HF progression. ACE inhibitors, angiotensin receptor blockers (ARBs), and β-blockers have been proven to provide cardiovascular benefit to patients at any point during HF development. However, β-blockers have been underused, possibly because of perceptions of complex management, adverse events, a contraindication in patients with LVD, or negative effects on short-term clinical outcomes.[12] Use of β-blockers in the treatment of the various HF stages is summarized in Table 2.[8] In this review, I discuss an evidence-based approach in supporting the role of β-blockers in each HF stage.

METHODS

A PubMed search of the years 1980 to 2008 was conducted to identify clinical trials that evaluated the efficacy of antihypertensive therapies (primarily β-blockers) for patients with any HF stage or hypertension. Search terms were *heart failure*, *hypertension*, β-*blocker* (including *atenolol*, *bisoprolol*, *bucindolol*, *carvedilol*, *labetalol*, *metoprolol*, *nebivolol*, or *propranolol*), *angiotensin-converting enzyme inhibitor* (*ACEI*), *angiotensin receptor blocker* (*ARB*), *calcium channel blocker*, AND *blood pressure*, *coronary artery disease*, *diabetes*, *efficacy*, *left ventricular dysfunction*, *metabolism*, *mortality*, *myocardial infarction*, or *stroke*.

TABLE 1. **New York Heart Association Classification System for Patients With Heart Failure**

Class	Symptoms
I	No limitation of physical activity; ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath)
II	Slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea
III	Marked limitation of physical activity; comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea
IV	Unable to perform any physical activity without discomfort; symptoms of cardiac insufficiency at rest; if any physical activity is undertaken, discomfort is increased

Data from Criteria Committee of the New York Heart Association.[11]

Larger studies that evaluated cardiovascular events and outcomes were given preference. Professional cardiology affiliations were used to identify guidelines.

STAGE A HF: PATIENTS AT RISK OF DEVELOPING HF

Stage A of the ACC/AHA classification is "pre-HF." Patients in this stage have no structural heart disease or HF symptoms but are at high risk of developing HF because of the presence of risk factors such as coronary artery disease (CAD), hypertension, diabetes, obesity, exposure to cardiotoxic drugs, excessive alcohol consumption, rheumatoid disease, or family history of cardiomyopathy[13] (Figure 1).[8] Affirmation of these risk factors as antecedent HF causes has been an important contribution of the ACC/AHA staging system because it has focused attention on preventing HF development through more aggressive modification of these risk factors. ACE inhibitors and/or ARBs are recommended for treatment of hypertension with associated cardiovascular risk factors on the basis of clinical data showing reductions in end-organ damage, renal disease, first hospitalization for HF, and risk of cardiovascular death.[8] Current evidence shows that β-blockers also modify the risk of hypertension, CAD, and diabetes in HF development, although using β-blockers to treat hypertension is controversial, possibly because individual agents provide varying benefits, in part, due to pharmacological differences.[12,14-18]

TABLE 2. **β-Blockers for the Treatment of Various Stages of HF**[a]

β-Blocker	Stage A	Stage B	Stage C
Acebutolol	HTN	NA	NA
Atenolol	HTN	Post-MI	NA
Betaxolol	HTN	NA	NA
Bisoprolol[b]	HTN	NA	HF
Carteolol	HTN	NA	NA
Carvedilol[c]	HTN	Post-MI LVSD	HF, Post-MI LVSD
Labetalol	HTN	NA	NA
Metoprolol succinate	HTN	NA	HF
Metoprolol tartrate	HTN	Post-MI	NA
Nadolol	HTN	NA	NA
Penbutolol	HTN	NA	NA
Pindolol	HTN	NA	NA
Propranolol	HTN	Post-MI	NA
Timolol	HTN	Post-MI	NA

[a] HF = heart failure; HTN = hypertension; LVSD = left ventricular systolic dysfunction; MI = myocardial infarction; NA = not approved.
[b] Bisoprolol has not been approved by the US Food and Drug Administration for HF.
[c] Both formulations of carvedilol (carvedilol and carvedilol phosphate, once daily) are indicated for HTN, post-MI LVSD, and HF.
Adapted from *Circulation*,[8] with permission.

HYPERTENSION

Controlling hypertension is essential across all HF stages. Of all HF cases from the original Framingham data, 91% were preceded by hypertension,[19] and hypertension was found to account for a relatively greater proportion of symptomatic HF in women, African Americans, and elderly persons.[20] Multiple large, controlled studies have shown that optimal blood pressure control decreases HF risk. For example, during an 8-year follow-up in the UK Prospective Diabetes Study Group trial, tight blood pressure control reduced HF risk by 56% compared with less-tight control.[21]

Among agents that can be used to control hypertension, diuretics, ACE inhibitors, ARBs, and β-blockers have been shown to be effective in HF prevention. However, calcium channel blockers, which can cause peripheral edema, have not been shown to be effective in HF prevention.[8,22] A meta-analysis of multiple long-term randomized trials that evaluated β-blockade use across the spectrum of cardiovascular disease found a 42% reduction in the risk of developing congestive HF in patients randomized to β-blockade regardless of the initial indication for β-blocker treatment.[23] β-Blockers that are suggested for hypertension treatment in patients with stage A HF based on the ACC/AHA guidelines are listed in Table 2.[8]

Recently, some hypertension guideline committees and published reviews have recommended that β-blockers not be listed as first-line therapy for uncomplicated hypertension. However, β-blockers are recommended for patients with diabetes and symptomatic angina, those at high risk of CAD, and patients who have had a myocardial infarction (MI).[16,17,24-26] Studies such as the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial—Blood Pressure Lowering Arm) found that β-blockers control hypertension poorly compared with other treatments and increase the risk of stroke and other coronary events.[27] Recent reviews and meta-analyses have speculated that β-blockers may be less effective in reducing central aortic pressure than other antihypertensive classes, possibly because heart rate

slowing from β-blockers may facilitate greater central pulse pressure amplification.[16-18] A meta-analysis of 9 studies of 68,222 patients with hypertension reported that the comparatively lower heart rate achieved with β-blockers vs other antihypertensive classes or placebo was associated with an increased risk of MI or HF ($P<.0001$ for both) and a possible increased risk of stroke ($P=.06$).[28] A separate meta-analysis of 12 trials of 112,177 patients with hypertension reported that β-blockers provided similar overall blood pressure efficacy compared with other antihypertensive classes and resulted in the same benefits for HF risk reduction (risk ratio, 1.0; 95% confidence interval [CI], 0.92-1.08).[29] Thus, use of β-blockers to treat hypertension is still controversial. Many of the reports included in the meta-analysis previously mentioned included only the most commonly prescribed older β-blockers, such as atenolol, and thus might not adequately represent the newer β-blockers.

Atenolol has been described as providing a "pseudo antihypertensive effect" because it lowers peripheral arterial pressure but not central aortic pressure and therefore may not reduce the pressure to which the heart and brain are exposed.[30] This theory is based on the observation that atenolol provides only β_1-blockade, allowing unopposed α-mediated reflex vasoconstriction. Peripheral vasoconstriction likely magnifies reflection of the central systolic pressure wave and tends to augment central aortic pressure. The CAFE (Conduit Artery Functional Endpoint) study (substudy of ASCOT-BPLA) compared central aortic pressure and brachial artery pulse pressure in patients treated with atenolol (50-100 mg/d) and thiazide vs amlodipine and perindopril. Although both treatments lowered pulse pressure to a similar degree, atenolol was much less effective in lowering central aortic pressure, and the risk of stroke and other cardiovascular events was higher in the atenolol group.[31] However, INVEST (International Verapamil SR/Trandolapril Study) compared atenolol (50 mg twice daily) with ACE inhibitors and found no difference in the risk of coronary events.[32] An important difference in these 2 studies is that ASCOT-BPLA used once-daily atenolol dosing, whereas INVEST used twice-daily dosing. The dosing differences may have contributed to the differences in clinical outcomes observed with atenolol.

β-Blockers are a diverse group of compounds with varying degrees of specificity to α-, β_1-, and β_2-receptor blockade. Selective β_1-blockers and nonselective β-blockers permit α-mediated peripheral vasoconstriction. Comprehensive β-blockers, such as carvedilol and labetalol, enhance vasodilatation through α-blockade. Bucindolol and nebivolol also enhance peripheral vasodilatation, with nebivolol exerting its effects possibly via the L-arginine/nitric oxide pathway.[14] The vasodilatory effects of carvedilol and nebivolol may lead to lower central aortic pressure.[14,15] Compared with other β-blockers, both carvedilol and nebivolol are less effective for lowering heart rate.[18] Clinical judgment should be used in treating patients with reactive airways disease who are dependent on β_2-agonists. A selective β_1-blocker may be more appropriate than a nonselective β-blocker, such as propranolol, or a comprehensive α- and β-blocker, such as carvedilol.[33] Additionally, clinical judgment should be used in treating patients with hypotension or syncope. Peripheral vasodilatation due to the comprehensive adrenergic blockers (α, β_1, and β_2) may worsen these conditions.[34]

Diabetes

Diabetes, especially in the presence of hypertension, is strongly associated with the development of HF,[35,36] and the prevalence of hypertension is often increased in the presence of diabetes.[37] These 2 comorbid conditions exert an additive effect in worsening LVD.[38] A population-based survey (Strong Heart Study) revealed that diabetes was independently associated with abnormal left ventricular relaxation, similar to the abnormality seen with hypertension. More severely impaired relaxation occurred in the presence of both diabetes and hypertension compared with either condition alone. These observations have established hypertension and diabetes as significant risks for development and progression of HF (Figure 2).[20] The Framingham Heart Study observed that HF was twice as common in men with diabetes and 3 to 4 times more common in women with diabetes compared with nondiabetic individuals.[39] The SOLVD (Studies of Left Ventricular Dysfunction) registry found a history of diabetes in almost one-fourth of 6273 patients with HF and/or reduced LV function (<45%).[40] Chae et al[41] showed that increases from baseline hemoglobin A_{1c} (HbA_{1c}) levels were linearly associated with increasing risk of developing HF in both diabetic and nondiabetic patients, with a 15% increase in HF risk for every 1% increase in HbA_{1c}. This was also observed in a study of more than 48,000 diabetic patients from the Kaiser Permanente Medical Care Program registry (2.2-year follow-up), in which every 1% HbA_{1c} increase was associated with an 8% increase in the risk of new HF.[42] Moreover, impaired systolic function and diastolic function are observed in noninvasive assessments of left ventricular performance and are inversely correlated with HbA_{1c}.[43,44]

The ACC/AHA guidelines assert that ACE inhibitors and ARBs have been "most notable with respect to a reduction in the onset of HF and diabetes."[8] The double-blind ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial), which randomly assigned hypertensive patients to receive chlorthalidone, amlodipine, or lisinopril, found that patients receiving

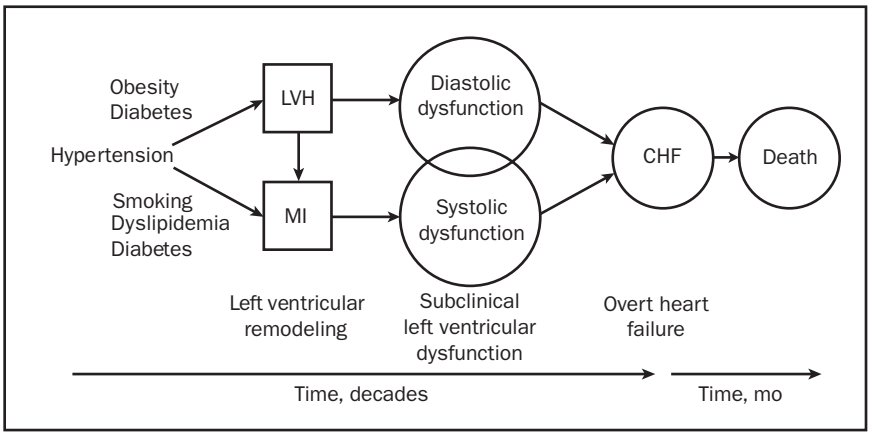

FIGURE 2. Progression of hypertension and other early risk factors for heart failure. CHF = congestive heart failure; LVH = left ventricular hypertrophy; MI = myocardial infarction. From *Arch Intern Med*,[20] with permission.

lisinopril experienced the lowest incidence of new-onset diabetes. At 4-year follow-up, 11.6%, 9.8%, and 8.1% of the nondiabetic patients had developed new-onset diabetes among the chlorthalidone, amlodipine, and lisinopril arms, respectively.[22] However, the more recent DREAM (Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication) trial showed that the effect of ramipril was similar to that of placebo on the incidence of new-onset diabetes or death during a 3-year study of 5269 participants without cardiovascular disease but with impaired fasting glucose tolerance levels.[45]

In diabetic patients, ACE inhibitors have been shown to be effective in limiting the risk of cardiovascular complications. The ABCD (Appropriate Blood Pressure Control in Diabetes) trial compared blood pressure control with nisoldipine and enalapril in 470 hypertensive patients with diabetes.[46] After 5 years of follow-up with risk adjustment, nisoldipine was associated with a higher incidence of MI (relative risk [RR], 9.5; 95% CI, 2.3-21.4) compared with the ACE inhibitor. The HOPE (Heart Outcome Prevention Evaluation) trial showed that, in patients at high risk of cardiovascular events, ramipril significantly reduced the likelihood of mortality from MI, stroke, or other cardiovascular causes (RR, 0.78; 95% CI, 0.70-0.86; $P<.001$).[47]

Some physicians have been reluctant to prescribe β-blockers because they cause weight gain and because of the potential for increasing insulin resistance and worsening lipid metabolism.[48] The ARIC (Atherosclerosis Risk in Communities) study found that using β-blockers to lower blood pressure caused a 28% increase in the risk of developing diabetes, independent of the effect on hypertension.[49] The use of a thiazide diuretic did not increase diabetes risk. In the LIFE (Losartan Intervention for Endpoint Reduction) study, the risk of developing new-onset diabetes was 25% higher with atenolol vs losartan treatment ($P<.001$).[50] Moreover, losartan was associated with higher insulin sensitivity than atenolol.[50,51] Recent reviews and meta-analyses of predominately older β-blockers report an increase in the risk of new-onset diabetes of 22% to 31% compared with nondiuretic antihypertensive agents.[16,17] However, not all β-blockers may have these effects.

Unlike β_1-selective β-blockers, the combined α_1-, β_1-, and β_2-adrenergic blocker carvedilol has been shown to have a neutral effect on insulin sensitivity and on triglyceride and cholesterol levels in hypertensive patients.[52-54] In a 3-month randomized, controlled trial that compared carvedilol with metoprolol tartrate in 72 nondiabetic patients with hypertension and impaired insulin sensitivity, metoprolol tartrate decreased insulin sensitivity by an additional 14%, whereas carvedilol increased insulin sensitivity by 9%.[54] Additionally, triglyceride levels increased and high-density lipoprotein cholesterol (HDL-C) levels decreased with metoprolol tartrate but remained unchanged with carvedilol. In a randomized, double-blind 24-week study of 45 patients with diabetes and hypertension, carvedilol improved glucose disposal by 20%, decreased triglyceride levels by 20%, increased HDL-C levels by 7%, and lowered HbA_{1c} levels by 0.1%, whereas atenolol decreased glucose disposal by 16%, increased triglyceride levels by 12%, decreased HDL-C levels by 5%, and increased HbA_{1c} levels by 0.3% ($P<.001$).[53] Although the clinical importance of these findings remains unclear, the data support the concept that different β-blockers may have varying effects on carbohydrate metabolism.

The GEMINI (Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives) trial is the only large-scale trial (N=1235) of metabolic end points to compare β-blocker use in patients with hyperten-

sion and diabetes.[52] In this 35-week, double-blind, parallel-group trial, patients were randomized to either metoprolol tartrate or carvedilol twice daily for blood pressure control. Most patients (about 98%) continued to receive ACE inhibitor/ARB therapy; open-label hydrochlorothiazide and a dihydropyridine calcium channel antagonist were added, if needed, for blood pressure control. No significant differences in blood pressure level or percentage of patients reaching goal were observed. Metoprolol tartrate increased HbA_{1c} values from baseline by 0.15% ($P<.001$), but carvedilol caused no increase in HbA_{1c} ($P=.004$ for mean treatment difference). Additionally, carvedilol significantly improved insulin sensitivity from baseline (–9%; $P=.004$), which was not observed with metoprolol tartrate (–2%; $P=.48$). Furthermore, a 14% decrease in the albumin/creatinine ratio was observed with carvedilol compared with a 2.5% increase with metoprolol tartrate (treatment difference, $P=.003$). Despite these differing metabolic effects, no differences in clinical outcomes were observed.

Only small trials have investigated the relationship between metoprolol succinate and insulin resistance, with varying results. In 1 trial, after 12 weeks of metoprolol succinate plus hydrochlorothiazide therapy, no significant changes occurred in insulin clamp measures of insulin sensitivity.[55] In contrast, in another trial of patients with hypertension who received 6 months of metoprolol succinate, the insulin sensitivity index was significantly reduced by 22% ($P=.0025$), followed by significant increases in HbA_{1c} levels of 0.3% ($P=.04$).[56]

Coronary Artery Disease

The ACC/AHA guidelines promote lifestyle, diet, and evidence-based pharmacological interventions to control lipids, hypertension, and diabetes in an effort to prevent atherosclerosis, CAD, and HF and to reduce cardiovascular mortality.[8] Use of ACE inhibitors has reduced mortality in patients with CAD, in both the presence and the absence of HF or LVD. This was observed in the SAVE (Survival and Ventricular Enlargement) trial, which enrolled patients post-MI with an LVEF of 40% of less[57]; the SOLVD trial, which enrolled both symptomatic and asymptomatic patients with an LVEF of 35% of less[58]; and the HOPE trial, which enrolled patients at risk of cardiovascular events in the absence of LVD at baseline. ACE inhibitors are thought to retard atherogenesis through neurohormonal, anti-inflammatory, and endothelial mechanisms.[59]

In contrast, β-blockers may exacerbate CAD by unfavorable lipid metabolism effects. Traditional β-blockers reportedly increase triglyceride levels and decrease HDL-C levels.[60,61] However, the combined α_1-, β_1-, and β_2-adrenergic blocker carvedilol has shown no adverse effects on total cholesterol, HDL-C, triglyceride, and HbA_{1c} levels, as discussed previously.[52-54] The ACC/AHA guidelines specifically recommend prescribing an ACE inhibitor or ARB to prevent HF in high-risk patients.[8] The guidelines note that, "Ultimately, an appropriate antihypertensive regimen frequently consists of several drugs used in combination," an observation supported by several studies. When an antihypertensive regimen is being devised, therapeutic choices for optimal blood pressure control should be influenced by comorbid conditions. An ACE inhibitor followed by a β-blocker is an important treatment strategy to consider for patients at high risk of developing HF, such as those with hypertension.[26]

STAGE B HF: ASYMPTOMATIC PATIENTS WITH STRUCTURAL HEART DISEASE

The distinguishing characteristic of stage B HF is LVD development that occurs in response to an injury or chronic stress on the myocardium, as in patients who have had an MI. Stage B includes patients with asymptomatic abnormalities of cardiac structure (hypertrophy, dilatation, fibrosis) or function (systolic or diastolic impairment).[8] This stage correlates with the NYHA functional class I. The development of LVD is often progressive, even in the absence of a new insult to the heart.[8] Such patients should be treated with β-blockers and ACE inhibitors regardless of ejection fraction or presence of HF. Patients with stage B HF who cannot tolerate an ACE inhibitor may be treated with an ARB.

Depending on injury extent, clinical evidence of HF occurs in 2% to 20% of patients within the first 4 weeks after an MI.[20] The Framingham Heart Study found that 49% of patients with asymptomatic LVD had had an MI.[62] Acute loss of cardiac muscle and associated decrement in contractility lead to activation of compensatory mechanisms, including neurohormonal and adrenergic system activation resulting in peripheral vasoconstriction, salt and water retention, and increased contractility of noninfarcted myocardium (Figure 3).[63,64] These changes help maintain vital organ perfusion and augment cardiac output, but chronic activation of the sympathetic nervous system and renin-angiotensin-aldosterone system is toxic to cardiomyocytes.[2] Remodeling, including increases in left ventricular end-systolic and end-diastolic volumes (dilatation) and wall thickness (hypertrophy), occurs over time and leads to increased left ventricular sphericity, further ejection fraction decreases, and emergence of clinical HF.[1] Although patients often progress from asymptomatic to symptomatic stages, sudden death can occur at any time.[8] The interrelated roles of coronary disease progression, neurohormonal activation, and remodeling in the development of LVSD are depicted in Figure 3.[64]

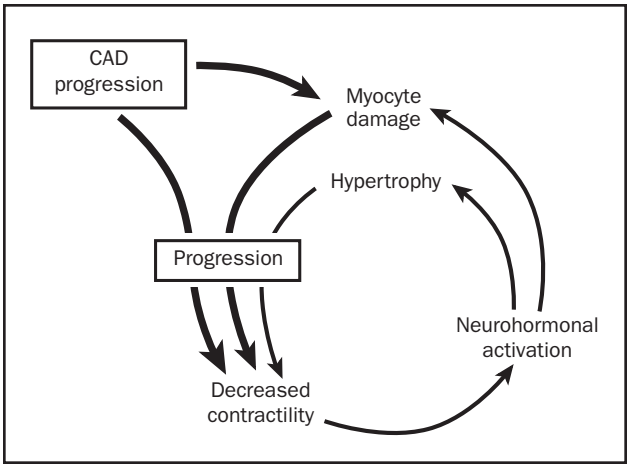

FIGURE 3. Interrelated roles of coronary artery disease (CAD) progression, neurohormonal activation, and remodeling in the development of left ventricular systolic dysfunction. From *Circulation*,[64] with permission.

β-Blockers may promote reverse remodeling of the ventricle in patients with asymptomatic LVSD, prevent progression to symptomatic HF, and improve outcomes.[8] These observations are based on several trials that have evaluated β-blockers in patients with asymptomatic LVSD. Post hoc analysis of the SOLVD-Prevention Trial (asymptomatic patients with an LVEF ≤35%) showed that 25% of patients with LVD who were receiving β-blockers and ACE inhibitors had significantly lower rates of mortality due to HF than those not receiving β-blockers (*P*=.003).[63] Retrospective analysis of data from the SAVE trial also found that patients who received β-blockers had a 30% lower risk of death and a 21% lower rate of progression to overt HF, a benefit that was independent of ACE inhibitor use in the trial.[65]

The CAPRICORN (Carvedilol Post-Infarct Survival Control in Left Ventricular Dysfunction) study was a randomized, placebo-controlled clinical trial of carvedilol in 1959 post-MI patients with reduced LVEF (mean, 33%; 50% asymptomatic for HF).[66] Nearly all the patients were receiving ACE inhibitors, and 46% underwent thrombolysis or percutaneous transluminal coronary angioplasty. During an average follow-up of 1.3 years, carvedilol reduced mortality risk by 23% (*P*=.031).[66] Carvedilol was equally effective in patients with or without HF symptoms. In a CAPRICORN subset analysis of asymptomatic patients, carvedilol decreased the risk of all-cause mortality by 31%.[67,68] In a post hoc review of CAPRICORN adverse events, carvedilol with an ACE inhibitor appeared to significantly suppress ventricular and atrial arrhythmias in post-MI patients with LVSD.[69] Compared with placebo, carvedilol reduced the incidence of atrial fibrillation (hazard ratio, 0.41; 95% CI, 0.25-0.68; *P*=.0003).

β-Blockers may slow progression of HF in stage B patients by reversing progressive cardiac remodeling. An echocardiographic CAPRICORN substudy of 127 patients found that carvedilol reduced left ventricular systolic volumes by 9.2 mL compared with placebo (*P*=.023). Additionally, after 6 months of treatment, patients receiving carvedilol had a statistically significant 3.9% increase in LVEF compared with those receiving placebo (*P*=.015).[70]

The CARMEN (Carvedilol ACE Inhibitor Remodeling Mild CHF Evaluation) trial assigned 572 patients with mild, stable HF (approximately 9%, 65%, and 26% of patients were classified in NYHA classes I, II, and III, respectively) to treatment with carvedilol alone, enalapril alone, or both and found that carvedilol, alone or with enalapril, resulted in greater reverse remodeling than enalapril monotherapy.[71] Carvedilol alone (target, 25 mg twice daily) significantly reduced left ventricular end-systolic volume index by 2.8 mL/m^2 from baseline (*P*=.018). Combined enalapril and carvedilol therapy reduced left ventricular end-systolic volume index by 6.3 mL/m^2 (*P*=.0001).

The recently published REVERT (Reversal of Ventricular Remodeling with Toprol-XL) trial, a double-blind, placebo-controlled study, assessed efficacy of 50-mg (low-dose) and 200-mg (high-dose) metoprolol succinate tablets added to standard therapy for 12 months on reversing cardiac remodeling in 164 asymptomatic patients with HF (NYHA class I) and LVSD.[72] The 200-mg group had a significant decrease of 14.5 mL/m^2 in left ventricular end-systolic volume index compared with baseline (*P*<.05) and with placebo (*P*<.05), whereas the 50-mg group had no change compared with placebo.

STAGE C HF: SYMPTOMATIC PATIENTS WITH STRUCTURAL HEART DISEASE

Stage C patients have current or previous HF symptoms associated with cardiovascular structural abnormalities.[8] Signs can include evidence of volume overload, such as edema and pulmonary congestion, or symptoms such as dyspnea on exertion and fatigue. This stage corresponds to NYHA classes II to IV. Several large-scale, randomized clinical trials have documented the benefits of bisoprolol, carvedilol, and metoprolol succinate in the treatment of symptomatic patients with HF and LVSD (Table 3[6,7,9,73-76] and Table 4[8,77,78]). The evidence-based benefits of β-blockers for symptomatic patients with HF include reductions in all-cause and cardiovascular mortality, fewer sudden deaths, fewer stroke deaths, decreases in the risk of hospitalization, improved LVEF and clinical status, and deceleration of disease progression. BEST (β-Blocker Evaluation of Survival Trial), the study that evaluated bucindolol in HF, was terminated because there was no significant

TABLE 3. **Large-Scale Studies of Evidence-Based β-Blockers in Heart Failure**[a]

Trial	Agent	No. of patients	NYHA class	Mean follow-up (mo)	Annual placebo mortality rate (%)	Mortality risk reduction (%)	Target dose (mg)	Mean daily dose (mg)
CIBIS-II[6]	Bisoprolol	2647	III-IV	15	13.2	↓34	10 once daily	10[b]
MERIT-HF[7]	Metoprolol succinate	3991	II-IV	12	11.0	↓34	200 once daily	159
US carvedilol trials[9]	Carvedilol	1094	II-IV	6.5 (median)	7.8	↓65[c]	25-50 twice daily	45
ANZ[73]	Carvedilol	415	II-III	19	12.5	↓26	25 twice daily	41
COPERNICUS[74,75]	Carvedilol	2289	III-IV	10.4	19.7	↓35	25 twice daily	37
	Carvedilol	1511	II-IV	58	NR	↓27 (carvedilol vs metoprolol)	25 twice daily	41.8
COMET[76]	Metoprolol succinate	1518	II-IV	58	NR	NR	50 twice daily	85

[a] ANZ = Australia/New Zealand Heart Failure Research Collaborative Group; CIBIS-II = Cardiac Insufficiency Bisoprolol Study II; COMET = Carvedilol or Metoprolol European Trial; COPERNICUS = Carvedilol Prospective Randomized Cumulative Survival; MERIT-HF = Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; NR = not reported; NYHA = New York Heart Association.
[b] Most common dose achieved in study.
[c] Study design did not constitute a mortality trial.

difference in mortality (primary end point) compared with placebo, although subgroup analyses suggested populations that might benefit from bucindolol.[79] All these trials were conducted with ACE inhibitors and diuretic therapy.

The US Carvedilol Heart Failure Program enrolled 1094 patients with chronic HF with an LVEF of 35% or less (mean LVEF, 23%) in a double-blind, placebo-controlled, stratified program in which patients were assigned to 1 of the 4 treatment protocols on the basis of their exercise capacity.[9] Overall, a 65% decrease in all-cause mortality was found ($P<.001$) when carvedilol was compared with placebo. Because of the marked effect on mortality, the program was terminated early. This decrease in mortality was observed for both sudden death (placebo, 3.8%; carvedilol, 1.7%) and death due to progressive HF/pump failure (placebo, 3.3%; carvedilol, 0.7%). A 27% reduction in the risk of hospitalization for any cardiovascular cause with carvedilol ($P=.036$) and a 38% reduction in HF hospitalizations ($P=.041$) were also noted.[9,80] Length of stay for HF admissions and the number of days in the intensive care/coronary care unit were reduced by 37% ($P=.03$) and 83% ($P=.001$), respectively, in the carvedilol-treated group.[80] In one of the studies from the US Carvedilol Heart Failure Program that included 366 patients with mild HF who were randomized to either carvedilol (6.25-50.0 mg twice daily) or placebo, patients treated with carvedilol had a statistically significant LVEF improvement compared with patients receiving placebo (10% vs 3%, respectively; $P<.001$) at 12-month follow-up.[81] A similar benefit for reductions in risk of mortality and hospitalization was observed in the ANZ (Australia/New Zealand Heart Failure Research Collaborative Group) trial, in which 415 patients with chronic, stable HF were randomly assigned to carvedilol or placebo and followed up for an average of 19 months.[73] Carvedilol resulted in a 26% reduction in the risk of all-cause mortality or hospitalization (95% CI, 0.57-0.95) compared with placebo. End-diastolic and end-systolic dimensions decreased by 1.7 mm ($P=.06$) and 3.2 mm ($P=.001$), respectively, resulting in a 5.3% ($P<.0001$) increase in LVEF in carvedilol-treated patients.

The MOCHA (Multicenter Oral Carvedilol Heart Failure Assessment) trial, 1 of the 4 treatment protocols in the US Carvedilol Heart Failure Program, showed that carvedilol may reduce remodeling in patients with mild to moderate HF compared with placebo.[77] Carvedilol was associated with dose-related LVEF improvements (5, 6, and 8 units in the 6.25-mg, 12.5-mg, and 25-mg twice-daily groups, respectively); each treatment group was statistically different from placebo ($P\leq.005$, all doses) and showed a significant dose-linear response ($P<.01$). This study also found dose-related reductions in mortality compared with placebo: 6.25-mg group (RR, 0.356; 95% CI, 0.127-0.998; $P<.05$), 12.5-mg group (RR, 0.416; 95% CI, 0.158-1.097; $P=.07$), and 25-mg group (RR, 0.067; 95% CI, 0.009-0.51; $P<.001$).

TABLE 4. **Recommended Dosing of Evidence-Based β-Blockers for Patients With Heart Failure**

Evidence-based β-blocker	Initial dose (mg)	Maximal dose (mg)
Bisoprolol	1.25 once daily	10 once daily
Carvedilol[a]	3.125 twice daily	25 twice daily
Carvedilol controlled release	10.0 once daily	80 once daily
Metoprolol succinate	12.5-25.0 once daily	200 once daily

[a] For mild to moderate heart failure, efficacy begins with a 6.25-mg dose taken twice daily and continues across the dose range from 6.25-25.0 mg twice daily.
Data from *Circulation*,[8] *Circulation*,[77] and *Expert Opin Pharmacother*.[78]

MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in Chronic Heart Failure), the largest trial evaluating β-blockade efficacy in HF, is a double-blind, placebo-controlled trial of the efficacy of controlled-release/extended-release metoprolol succinate in 3991 patients with symptomatic HF (NYHA classes II to IV; LVEF ≤40%) stabilized with standard treatment.[7] After 12-month follow-up, metoprolol succinate reduced all-cause mortality risk by 34% (*P*=.0062) and reduced total mortality or all-cause hospitalization risk by 19% (*P*<.001).[7,82] Metoprolol succinate also reduced risk of sudden death by 41% (*P*<.001) and risk of death due to worsening HF by 49% (*P*=.002).[7,82] Compared with placebo, metoprolol succinate reduced the total number of days in the hospital due to all causes by 17% and due to HF by 36%.

CIBIS-II (Cardiac Insufficiency Bisoprolol Study II) compared the effects of bisoprolol, a selective β_1-antagonist, with placebo in 2647 symptomatic patients (NYHA class III or IV; LVEF ≤35%) receiving ACE inhibitors and diuretics.[6,83] During a mean of 1.3 years, bisoprolol significantly reduced all-cause mortality by 34% vs placebo (*P*<.0001).[6] Bisoprolol also resulted in significantly fewer cardiac deaths (*P*=.0049), hospital admissions for any cause (*P*=.0006), and hospital admissions for worsening HF (32% reduction compared with placebo; *P*<.0001). In an open-label study of 201 patients, mean LVEF improved after 3 months of therapy (31% at baseline and 41% after bisoprolol; *P*<.0001) with the maximal tolerated dose of bisoprolol (mean ± SD dose, 8.8±2.4 mg/d). Bisoprolol significantly decreased end-systolic and end-diastolic left ventricular diameters (4.9 mm and 2.3 mm, respectively; *P*<.0001 for both) and volumes (33 mL and 28 mL, respectively; *P*<.0001 for both) from baseline.[84]

In BEST, the effects of bucindolol, a nonselective β-adrenergic antagonist and mild vasodilator, were compared with placebo in 2708 symptomatic patients (NYHA class III or IV; LVEF ≤35%) receiving optimal therapy including ACE inhibitors.[79] After a mean 2-year follow-up, bucindolol treatment resulted in a nonsignificant reduction in all-cause mortality vs placebo (hazard ratio, 0.90; *P*=.13). However, bucindolol significantly reduced cardiovascular mortality by 14% vs placebo (*P*=.04).

A substudy of BEST (n=79) revealed that, among patients with contractile reserve as assessed by responsiveness to dobutamine infusion, bucindolol had a significantly beneficial effect on survival.[85] Patients lacking contractile reserve had higher baseline norepinephrine levels and a greater decrease in norepinephrine levels after bucindolol treatment compared with patients who had contractile reserve, suggesting that higher adrenergic drive exists in patients without contractile reserve and that bucindolol produces greater sympatholytic effects in these patients.

Another substudy of BEST (n=1040) showed that a common DNA polymorphism in the β_1-adrenergic receptor gene (arginine [Arg] 389 to glycine [Gly]; n=94 homozygous for Gly) predicts responsiveness to bucindolol. Patients with Arg389Arg who received bucindolol had a 38% reduction in mortality compared with those who received placebo (*P*=.03), whereas patients with Arg389Gly had no treatment response from bucindolol.[86] This observation is forming the basis for a prospective pharmacogenomic registry study to randomize patients to bucindolol vs other β-blockers on the basis of the Arg 389 polymorphism.

In addition to placebo-controlled trials, COMET (Carvedilol or Metoprolol European Trial), a large-scale, head-to-head comparison between carvedilol and metoprolol tartrate, was performed in patients with mild to moderate HF (mean LVEF, 26%) who were randomized to receive either carvedilol (target dose, 25 mg twice daily) or metoprolol tartrate (target dose, 50 mg twice daily).[76] After a mean follow-up of 58 months, carvedilol significantly reduced all-cause mortality (RR, 17%; *P*=.0017), cardiovascular mortality (RR, 20%; *P*=.0004), and stroke mortality (RR, 66%; *P*=.0006) compared with metoprolol tartrate.[76,87] Carvedilol also had a 22% reduction in the risk of new-onset diabetes-related adverse events compared with those taking metoprolol (*P*=.048).[88] Debate has persisted regarding metoprolol tartrate as the comparator in COMET because the succinate form of metoprolol was used in the MERIT-HF study. Outcomes in patients who reached target doses of both drugs in COMET revealed no differences compared with overall trial results.[89] In a meta-analysis of 19 randomized controlled trials of 2184 patients with HF receiving carvedilol or metoprolol in which LVEF was measured before and after an average of 8.3 months of treatment, carvedilol increased LVEF 6.5% compared with placebo (±0.5%; *P*<.0001), and metoprolol increased LVEF 3.8% compared with placebo (±0.5%; *P*<.0001).[90] For the 4 trials included in the meta-analysis that were direct comparisons of carvedilol to metoprolol tartrate, carvedilol resulted in a significantly greater ejection fraction increase (8.9% for carvedilol vs 5.5% for metoprolol tartrate; *P*=.009).

ADVANCED STAGE C HF

Although substantial evidence in the medical literature supports β-blocker use in patients with mild to moderate HF, data are limited regarding the long-term safety and efficacy of β-blockers in patients with severe, chronic HF. However, marked mortality benefits were observed in COPERNICUS (Carvedilol Prospective Randomized Cumulative Survival Study), which evaluated carvedilol in 2289 patients with severe chronic HF (LVEF <25%).[74] The

carvedilol group had a 35% reduction in total mortality risk (*P*=.001), with a 1-year cumulative mortality risk of 18.5% in the placebo group and 11.4% in the carvedilol group. Carvedilol reduced the combined risk of death or hospitalization for a cardiovascular reason by 27% (*P*=.00002) and the combined risk of death or hospitalization for HF by 31% (*P*=.000004).[75] The carvedilol group spent 27% fewer days in the hospital for any reason (*P*=.0005) and 40% fewer days in the hospital for HF (*P*<.0001). Carvedilol-treated patients were also less likely than placebo-treated patients to experience a serious adverse event (*P*=.002), including worsening HF, sudden death, cardiogenic shock, or ventricular tachycardia. Within COPERNICUS, a very high-risk subgroup of 624 patients was identified (recent or recurrent cardiac decompensation [≥3 hospitalizations for HF within the previous year], need for intravenous inotropic or vasodilator therapy within 14 days before randomization, or baseline LVEF ≤15%).[75] Cumulative 1-year mortality risk for the placebo group of this high-risk population was 28.5% per patient-year of follow-up and was reduced by 39% in the carvedilol group (*P*=.009).[74] In 371 patients with LVEF of 15% or less at entry, carvedilol-associated improvements in clinical outcomes, including all-cause mortality and death or hospitalization for HF, were similar to those for patients with entry LVEF of greater than 15%.[91] This underscores the utility of β-blocker therapy, specifically carvedilol, even in patients with advanced chronic HF.

STAGE D HF: SEVERELY SYMPTOMATIC PATIENTS WITH STRUCTURAL HEART DISEASE

Stage D patients are often dependent on inotrope or device therapy. They are symptomatic at rest despite optimal medical therapy and are hospitalized recurrently.[8] Patients in NYHA class IV could be in ACC/AHA stage C or D depending on the degree of "extraordinary" support they require (ie, inotropes, left-ventricular assist device, etc).[8,26] No large-scale clinical trials have been performed of long-term pharmacotherapy for patients with stage D HF. These patients may tolerate only small doses of neurohormonal antagonists or may not tolerate even small doses. In the REMATCH (Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure) trial, 129 patients with end-stage HF who were ineligible for cardiac transplant were randomized to either a left ventricular assist device (n=68) or optimal medical management (n=61).[92] Baseline concomitant medications showed that approximately 56% of patients were able to tolerate ACE inhibitor therapy, and only 22% could tolerate β-blocker therapy. Consequently, physicians should exercise great care when considering β-blockers in patients with refractory HF. Treatment should be initiated in very low doses, and patients should be monitored closely for signs or symptoms of intolerance. Inability to tolerate ACE inhibitors or β-blockers predicts a particularly poor prognosis. In general, use of β-blockers should not be discontinued during hospitalization for HF unless patients are hemodynamically unstable, have evidence of end-organ hypoperfusion, and/or require intravenous positive inotropic support with β-adrenergic agonists.[8] For patients with end-stage HF who do not respond favorably to standard oral medical therapies, the following treatments should be considered: continuous intravenous positive inotropic therapy, mechanical circulatory support, referral for cardiac transplant, or hospice care.

CONCLUSION

β-Blockers are important in treating HF and have proved useful in reducing the likelihood of progression through the continuum of HF. They should be included in the therapeutic regimens of patients with asymptomatic LVSD to prevent progression to symptomatic HF, to slow or prevent remodeling of the ventricle, and to improve survival. Evidence-based β-blocker therapy (bisoprolol, carvedilol, or metoprolol succinate) in combination with standard therapy is a mainstay of treatment in all symptomatic patients with LVSD on the basis of large, well-designed outcomes trials showing survival benefits compared with placebo.

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